Effect of Gender and Genetic Mutations on Outcomes in Patients With Hypertrophic Cardiomyopathy

Hannah G. van Velzen, MD[a,*], Arend F.L. Schinkel, MD, PhD[a], Sara J. Baart, MSc[a], Roy Huurman, MD[a], Marjon A. van Slegtenhorst, PhD[b], Isabella Kardys, MD, PhD[a], and Michelle Michels, MD, PhD[a]

Gender has been proposed to impact the phenotype and prognosis of hypertrophic cardiomyopathy (HC). Our aims were to study gender differences in the clinical presentation, phenotype, genotype, and outcome of HC. This retrospective single-center cohort study included 1,007 patients with HC (62% male, 80% genotyped) evaluated between 1977 and 2017. Hazard ratios (HR) were calculated using multivariable Cox proportional hazard regression models. At first evaluation, female patients presented more often with symptoms (43% vs 35%, p = 0.01), were older than male patients (56 ± 16 vs 49 ± 15 years, p <0.001), and more frequently had hypertension (38% vs 27%, p <0.001), left ventricular outflow tract obstruction (37% vs 27%, p <0.001), and impaired left ventricular systolic (17% vs 11%, p = 0.01) and diastolic (77% vs 62%, p <0.001) function. Overall, the genetic yield was similar between genders (54% vs 51%, p = 0.4); however, in patients ≥70 years, the genetic yield was less in women (15% vs 36%, p = 0.03). During 6.8-year follow-up (interquartile range 3.2 to 10.9), female gender was not independently associated with all-cause mortality (HR 1.25 [0.91 to 1.73]), cardiovascular mortality (HR 1.22 [0.83 to 1.79]), heart failure-related mortality (HR 1.77 [0.95 to 3.27]), or sudden cardiac death (SCD) and/or aborted SCD (HR 0.75 [0.44 to 1.30]). Interventions and nonfatal clinical events did not differ between the genders. In conclusion, female patients with HC present at a more advanced age with a different clinical, phenotypic, and genetic status. There is no independent association between female gender and all-cause mortality, cardiovascular mortality, heart failure-related mortality, or SCD. **(Am J Cardiol 2018;122:1947−1954)**

Hypertrophic cardiomyopathy (HC) is a heterogeneous monogenic cardiac disease known to lead to sudden cardiac death (SCD), heart failure (HF), and atrial fibrillation with the increased risk of stroke.[1,2] Gender has been proposed to impact the age of onset and the phenotype of HC.[3−14] Studies that assessed gender and clinical outcome of HC report conflicting results.[5,15−17] Some studies report an independent association between female gender and all-cause mortality[16,17] or HF-related events.[15,16,18,19] Genotype has been shown to impact the phenotypic expression and clinical outcome of HC.[7,20−22] In the Netherlands, genetic counseling and testing is offered to all patients with HC, because it is covered by the national basic health-care program. The aim of this study was to assess gender-related differences in the genetic test results, clinical presentation, phenotype, and outcome of HC.

Methods

This single-center retrospective cohort study included 1,007 patients with HC who were evaluated at the Erasmus Medical Center in Rotterdam, the Netherlands, between the years 1977 and 2017. The diagnosis of HC was based on a maximal wall thickness (MWT) ≥15 mm in probands, ≥13 mm in relatives, and a z-score >2 in children, not solely explained by loading conditions. Patients with HC caused by Anderson-Fabry disease, Danon disease, Noonan syndrome, amyloidosis, or other confirmed metabolic or mitochondrial disorders or malformation syndromes were excluded. The study conforms to the principles of the Declaration of Helsinki. All patients gave informed consent for inclusion in the registry and local institutional review board approval was obtained.

Genetic counseling and testing was offered to all patients. Before the year 2012, genetic analysis consisted of direct sequencing of all coding exons and intron-exon boundaries of the following 8 genes: myosin-binding protein C (*MYBPC3*), -myosin heavy chain (*MYH7*), cardiac-regulatory myosin light chain (*MYL2*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), cysteine- and glycine-rich protein 3 (*CSRP3*), titin-cap and/or telethonin (*TCAP*), and α-tropomyosin (*TPM1*). From the year 2012, a next-generation-sequencing targeted approach including 48 to 52 cardiomyopathy-associated genes was used.

[a]Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; and [b]Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received June 11, 2018; revised manuscript received and accepted August 21, 2018.

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*Corresponding author: Tel: +31 10 70 35 994; fax: + 31 10 70 35 513.
E-mail address: h.g.vanvelzen@erasmusmc.nl (H.G. van Velzen).

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Classification of variants was done at time of initial testing. Variants were interpreted using a protocol adapted from the American College of Medical Genetics and Genomics recommendations,[23] and classified into 5 categories: (1) benign, (2) likely benign, (3) uncertain significance, (4) likely pathogenic, and (5) pathogenic. The potential pathogenicity of variants was assessed using Alamut Visual software (Interactive Biosoftware, Rouen, France), which integrates data from several large-scale population studies, evolutionary conservation of nucleotides and amino acids, in silico missense predictions (Align GVGD, SIFT, MutationTaster, and PolyPhen-2), and splicing prediction modules (SpliceSiteFinder-like, MaxEntScan, NNSPLICE, GeneSplicer, and Human Splicing Finder). The criteria for classification of variants included the allele frequency in the dbSNP/ESP/ExAC/GoNL (cutoff minor allele frequency 1% in at least 300 ethnically matched control alleles equals benign), predicted effects on splicing, the in silico prediction of effect on the protein, and previously described links to disease. Furthermore, segregation analysis in families with more affected patients and information considering presence in Human Gene Mutation Database (HGMD) Professional 2017.3 (Qiagen) is taken into account. Variant reclassifications during follow-up were registered, and variant classification as assessed at the end of follow-up was used for the analyses. Patients with a reclassified variant were informed about the reclassification and if applicable about the indication for renewed evaluation. Patients were considered genotype positive when the mutation was classified as likely pathogenic or pathogenic (classes IV and V).

Clinical assessment included medical history, physical examination, electrocardiography, and transthoracic echocardiography. Echocardiographic studies were analyzed according to the guidelines.[1,24,25] MWT, left atrial dimension, left ventricular (LV) end-diastolic diameter, and LV outflow tract velocity at rest were assessed.[1,24] LV outflow tract gradient was calculated with the Bernoulli equation. LV systolic function was categorized as good (LV ejection fraction >51%), mildly reduced (LV ejection fraction 41% to 51%), moderately reduced (LV ejection fraction 30% to 40%), and poor (LV ejection fraction <30%).[25] LV diastolic function was defined as normal, abnormal relaxation, pseudonormal, or restrictive filling, based on Doppler mitral inflow pattern parameters including early (E) and late (A) LV filling velocities, E/A ratio, and tissue Doppler imaging-derived septal early diastolic velocities (e').[26] Body surface area was calculated with the Du Bois & Du Bois formula.

Mortality data were retrieved from the civil service register in August 2017. Patients were followed for a median of 6.8 years (interquartile range 3.2 to 10.9; 7,363 total patient-years; 0.01% missing due to loss of follow-up). Patients who were lost to follow-up were censored at time of last follow-up. The cause of death was retrieved from the medical chart or the general practitioner and was obtained in 171 (87%) of mortality cases. Those with unknown causes of death were classified as all-cause mortality. Cardiovascular mortality included SCD and/or aborted SCD, HF-related death, postoperative death after a cardiac intervention, and stroke related death. SCD and/or aborted SCD was defined as: (1) instantaneous and unexpected death in patients who were previously in a stable clinical condition, or nocturnal death with no antecedent history of worsening symptoms; (2) resuscitation after cardiac arrest; or (3) appropriate implantable cardioverter defibrillator (ICD) intervention. Appropriate ICD intervention was defined as shock or antitachycardia pacing for ventricular fibrillation or ventricular tachycardia >200/min. Cardiac transplantation was considered HF-related mortality and patients were censored at the time of transplantation. The following nonfatal clinical events and interventions were registered: atrial fibrillation (paroxysmal, persistent, or permanent), stroke, transient ischemic attack, hospital admission for HF, septal reduction therapy (surgical myectomy and alcohol septal ablation), and ICD and pacemaker implantations. ICDs and pacemakers were implanted according to the guidelines.[1,24]

Calculations were performed using SPSS 21 (IBM, Armonk, New York) and R statistical software version 3.4.2 using packages nlme, lme4, survival, and smcfcs. Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data as median followed by interquartile range. To make comparisons between male and female patients, generalized linear mixed models were used, with random intercepts for family to account for family relatedness. Hazard ratios (HR) and 95% confidence intervals were calculated using univariable and multivariate Cox proportional hazard regression models with adjustment for family relatedness. For this purpose, the grouped jackknife method was used. Missing values of variables included in the multivariable analyses were imputed using 10 imputed datasets. All analyses were 2-tailed; p values <0.05 were considered significant.

Results

Baseline characteristics are presented in Table 1. Overall, there was a male predominance of 62%. The male predominance was present in all age groups, except in patients ≥70 years where women predominated (Figure 1). Male patients presented more often through routine medical examinations, and female patients presented more often with symptoms (Table 2). Female patients were significantly older than male patients both at time of diagnosis and at first evaluation (Table 1), also after excluding patients who presented through routine medical examinations (51 ± 18 vs 46 ± 17 years, p <0.001 and 55 ± 17 vs 49 ± 16 years, p <0.001, respectively). Female patients more frequently had a history of hypertension, and stroke and/or transient ischemic attack.

In patients ≥70 years old, the genetic yield was significantly less in female patients than in male patients (15% vs 36%, p = 0.03; Figure 2). Genes affected most frequently were *MYBPC3* (74%) and *MYH7* (14%; Figure 3). Other genes affected were *TNNI3* (3%), *TNNT2* (3%), *MYL2* (2%), *ALPK3* (1%), *TPM1* (0.7%), *MYL3* (0.7%), *CSRP3* (0.7%), *FHL1* (0.5%), *MIB1* (0.2%), and *TNNC1* (0.2%). There was no significant difference regarding the proportion of *MYBPC3* mutations (77% vs 69%, p = 0.08) or *MYH7* mutations (12% vs 18%, p = 0.09) in male or female patients, respectively. A complex genotype was present in 8 female patients (3%) and 8 male patients

Table 1
Baseline characteristics of 1,007 patients with hypertrophic cardiomyopathy according to gender

Variable	Overall (n = 1007)	Male (n = 620)	Female (n = 387)	p value
Age at evaluation (years)	52 ± 16	49 ± 15	56 ± 16	<0.001
<30	102 (10%)	68 (11%)	34 (9%)	0.26
30-50	338 (34%)	241 (39%)	97 (25%)	<0.001
>50	567 (56%)	311 (50%)	256 (66%)	<0.001
Age at diagnosis (years)	46 ± 17	44 ± 16	50 ± 19	<0.001
BSA (mm/m^2)	1.94 ± 0.23	2.05 ± 0.17	1.80 ± 0.17	<0.001
Arterial hypertension	310 (31%)	164 (27%)	146 (38%)	<0.001
Coronary artery disease	62 (6%)	43 (7%)	19 (5%)	0.21
Atrial fibrillation	213 (21%)	123 (20%)	90 (23%)	0.41
Septal reduction therapy	51 (5%)	30 (5%)	21 (5%)	0.67
ICD/PM implantation	47 (5%)	24 (4%)	23 (6%)	0.14
Stroke/TIA	61 (6%)	25 (4%)	36 (9%)	0.02
HF admission	24 (4%)	11 (3%)	13 (5%)	0.17
SCD/aborted SCD	16 (2%)	11 (2%)	5 (1%)	0.33
Medication				
Beta blockers	497 (49%)	292 (47%)	205 (53%)	0.07
Other anti-arrhythmic*	58 (6%)	31 (5%)	27 (7%)	0.19
Calcium antagonists	298 (30%)	183 (30%)	115 (30%)	0.95
Statins	196 (20%)	110 (18%)	86 (22%)	0.08
Diuretics	188 (19%)	84 (14%)	104 (27%)	<0.001
Aspirin	159 (16%)	80 (13%)	79 (20%)	0.001
Oral anticoagulants†	123 (12%)	64 (10%)	59 (15%)	0.02
ACE-i	124 (12%)	72 (12%)	52 (13%)	0.39
ATIIA	102 (10%)	54 (9%)	48 (12%)	0.06
ACE-i/ATIIA	222 (22%)	123 (20%)	99 (26%)	0.03
Genetic testing performed	810 (80%)	511 (82%)	299 (77%)	0.05
Pathogenic mutation	430 (53%)	277 (54%)	153 (51%)	0.39
Echocardiography				
MWT (mm)	19 ± 4	19 ± 4	18 ± 4	0.03
<13‡	8 (1%)	5 (1%)	3 (1%)	0.96
13-15	208 (21%)	108 (18%)	100 (26%)	0.001
16-19	428 (43%)	271 (45%)	157 (41%)	0.33
20-24	253 (26%)	167 (27%)	86 (23%)	0.09
25-29	68 (7%)	41 (7%)	27 (7%)	0.82
≥30	24 (2%)	17 (3%)	7 (2%)	0.35
MWT/BSA (mm/m^2)	9.6 ± 2.3	9.2 ± 2.0	10.3 ± 2.6	<0.001
LA (mm)	45 ± 8	45 ± 8	44 ± 8	0.001
LA/BSA (mm/m^2)	23.2 ± 4.1	22.5 ± 3.9	24.5 ± 4.1	<0.001
LVEDD (mm)	46 ± 6	47 ± 6	44 ± 6	<0.001
LVEDD/BSA (mm/m^2)	23.3 ± 3.4	22.7 ± 3.2	24.3 ± 3.5	<0.001
LVOT ≥ 30 mmHg§	300 (31%)	160 (27%)	140 (37%)	<0.001
Diastolic function				
Normal	285 (32%)	206 (38%)	79 (23%)	<0.001
Impaired relaxation	276 (31%)	147 (27%)	129 (38%)	<0.001
Pseudonormal filling	269 (30%)	169 (31%)	100 (30%)	0.60
Restrictive filling	55 (6%)	25 (5%)	30 (9%)	0.01
Systolic function				
Good	857 (87%)	543 (89%)	314 (83%)	0.01
Mildly reduced	95 (10%)	51 (8%)	44 (12%)	0.10
Moderately reduced	24 (2%)	8 (1%)	16 (4%)	0.01
Severely reduced	11 (1%)	7 (1%)	4 (1%)	0.87

Data are expressed as mean ± standard deviation or as absolute n (%). Generalized linear mixed models were used, with random intercepts for family to account for family relatedness.

ACE-i = ACE inhibitor; ATIIA = angiotensin II antagonist; BSA = body surface area; HF = heart failure; ICD = implantable cardioverter defibrillator; LA = left atrial size; LVEDD = left ventricular end diastolic diameter; LVOT = left ventricular outflow tract gradient; MWT = maximal wall thickness; PM = pacemaker; SCD = sudden cardiac death; TIA = transient ischemic attack.

* Includes flecainide, amiodarone, disopyramide, and ritmoforin.

† Includes 1 new oral anticoagulant.

‡ End-stage hypertrophic cardiomyopathy or postseptal reduction therapy.

§ At rest.

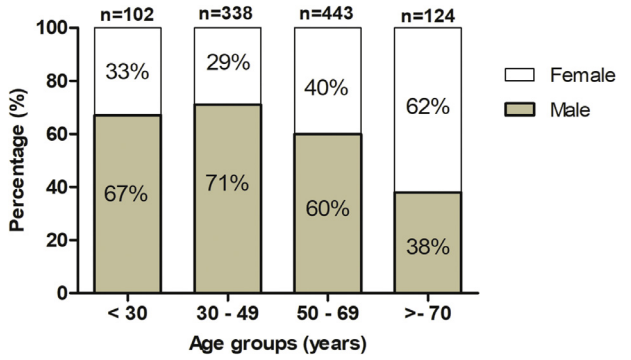

Figure 1. Male and/or female distribution among several age groups.

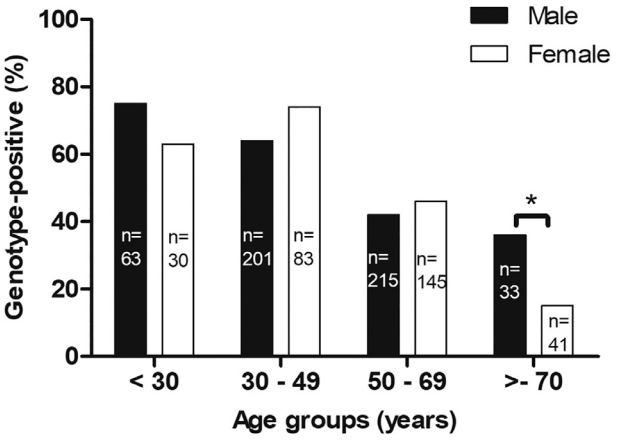

Figure 2. Genetic yield in male and female patients among several age groups. * indicates statistical significance with a $p < 0.05$.

(2%; $p = 0.3$), and included 8 homozygous mutations, 4 digenic, and 4 compound heterozygous mutations (Supplementary Table 1).

The MWT was higher in male patients, but the MWT corrected for body surface area was higher in female patients. Similar observations were made for left atrial dimension and LV end-diastolic diameter. A greater proportion of female patients had LV outflow tract obstruction, and systolic and diastolic function was more often impaired in female patients.

Mortality during a median 6.8-year follow-up (interquartile range 3.2 to 10.9) is presented in Table 3. In multivariable analysis (Tables 4 and 5), there was no independent association between gender and all-cause mortality (HR 1.25, $p = 0.16$), cardiovascular mortality (HR 1.22, $p = 0.31$), HF-related death (HR 1.77, $p = 0.08$), or SCD and/or aborted SCD (HR 0.75, $p = 0.31$). Missing values for the following variables were imputed: pathogenic mutation (20%), diagnosis by routine examination (18%), and body surface area (19%). Clinical follow-up was performed in 691 patients (69%); the remaining 316 patients (31%) were followed up in other hospitals. Interventions and nonfatal clinical events did not differ significantly between male and female patients (Table 6).

Table 2
Triggers for diagnosis in male and female patients with hypertrophic cardiomyopathy

Variable	Overall (n = 1007)	Male (n = 620)	Female (n = 387)	p value
Precordial murmur	149 (18%)	106 (20%)	43 (14%)	0.03
Abnormal ECG	111 (13%)	76 (15%)	35 (11%)	0.20
Other*	33 (4%)	20 (4%)	13 (4%)	0.75
Chest pain	145 (18%)	88 (17%)	57 (19%)	0.52
Dyspnea	112 (14%)	61 (12%)	51 (16%)	0.04
Palpitations	65 (8%)	30 (6%)	35 (12%)	0.004
Dizziness	37 (5%)	21 (4%)	16 (5%)	0.45
Syncope	39 (5%)	29 (6%)	10 (3%)	0.14
Fatigue	65 (8%)	27 (5%)	38 (13%)	<0.001
Sudden cardiac death†	11 (1%)	9 (2%)	2 (1%)	0.19
Atrial fibrillation	21 (3%)	11 (2%)	10 (3%)	0.33
Heart failure	5 (0.6%)	3 (0.6%)	2 (0.7%)	0.95
Acute myocardial infarction	11 (1%)	7 (1%)	4 (1%)	0.99
Stroke/TIA/embolism	5 (0.6%)	4 (0.8%)	1 (0.3%)	0.45
HC family screening	165 (20%)	103 (20%)	62 (20%)	0.81

Data are expressed as absolute n (%). Generalized linear mixed models were used, with random intercepts for family to account for family relatedness.

ECG = electrocardiography; HC = hypertrophic cardiomyopathy; TIA = transient ischemic attack.

* During preoperative screening, prescan, cardiac echo for other cardiac diseases.

† Two sudden cardiac deaths were not successfully resuscitated.

Discussion

In this study, we report the following gender differences in patients with HC: (1) at presentation, female patients were older, more frequently had a history of hypertension, and presented more frequently with symptoms; (2) female patients more frequently had an impaired systolic and diastolic function and more frequently exhibited LV outflow tract obstruction; (3) in the whole cohort, there was a male

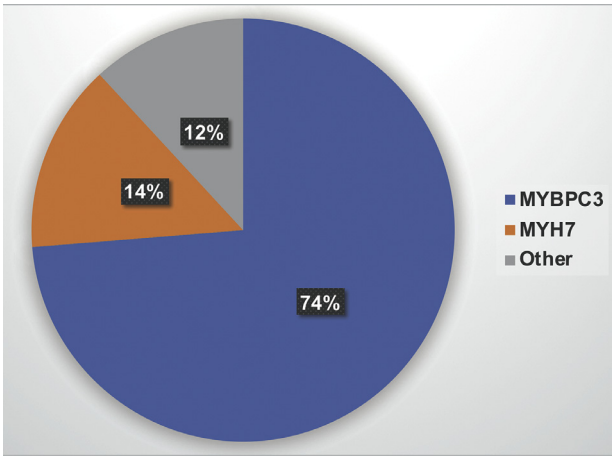

Figure 3. Distribution of pathogenic mutations in genotype-positive patients. *MYBPC3* = myosin-binding protein C; *MYH7* = -myosin heavy chain. *Other* includes mutations in cardiac troponin T (3%), cardiac troponin I (3%), cardiac-regulatory myosin light chain (2%), alpha-protein kinase 3 (1%), cysteine and glycine-rich protein 3 (0.7%), cardiac-essential myosin light chain (0.7%), α-tropomyosin (0.7%), four-and-a-half LIM domains protein 1 (0.5%), mindbomb E3 ubiquitin protein ligase 1 (0.2%), and cardiac troponin C (0.2%).

Table 3
Outcome differences in males and females with hypertrophic cardiomyopathy

Variable	Overall (n = 1005)	Male (n = 618)	Female (n = 387)	HR (95% CI)	p value
Follow-up	6.8 [3.2-10.9]	7.7 [3.5-11.1]	5.8 [2.3-10.1]	-	0.003
All-cause mortality	183 (19%)	91 (15%)	92 (24%)	1.85 (1.40-2.44)	<0.001
Cardiovascular mortality	110 (11%)	56 (9%)	54 (15%)	1.76 (1.22-2.54)	0.002
SCD/Aborted SCD	57 (6%)	37 (6%)	20 (5%)	0.99 (0.57-1.71)	0.97
Appropriate ICD shock	20 (2%)	15 (3%)	5 (1%)	0.63 (0.23-1.71)	0.36
Cardiac arrest	37 (4%)	22 (4%)	15 (4%)	1.23 (0.64-2.39)	0.53
HF related mortality	46 (5%)	19 (3%)	27 (7%)	2.50 (1.42-4.39)	0.001
Cardiac transplantation	16 (2%)	5 (1%)	11 (3%)	3.65 (1.22-10.9)	0.02
Stroke related death	4 (0.4%)	1 (0.2%)	3 (0.8%)	5.57 (0.55-56.8)	0.15
CIRD	6 (0.6%)	0 (0%)	6 (2%)	*	
Non-cardiac mortality	47 (5%)	22 (4%)	25 (7%)	2.11 (1.21-3.69)	0.009

Data are expressed as absolute n (%). Hazard ratios (HR) were calculated using univariable Cox proportional hazard regression models with adjustment for family relatedness.

For all-cause mortality, cardiovascular mortality, SCD/aborted SCD, and intervention-related death survival analyses, the patients with a history of SCD/aborted SCD were excluded.

CIRD = cardiac intervention-related death; HF = heart failure; ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death.

* Hazard ratio is not presented due to low number of events.

predominance, however, among patients ≥70-year-old women predominated in whom the genetic yield was significantly less than in male patients; and (4) during 6.8-year follow-up, there was no independent association between gender and all-cause mortality, cardiovascular mortality, HF-related mortality, or SCD and/or aborted SCD.

In this study, female patients had a delayed clinical presentation in comparison to male patients, also after excluding those who presented through routine medical examinations. Several previous studies have similarly reported a delayed clinical presentation in female patients with HC.[3,7,12,15–17,19] Olivotto et al[15] studied gender differences among 969 patients with HC and reported that female patients were 9 years old at time of initial evaluation, similar to Bos et al[7] who reported a 9-year delay in female patients among 382 patients with HC. Wang et al[16] reported a 3-year delay in female patients among 621 patients with HC, and recently Geske et al[17] reported a 7-year delay in female patients in a large cohort of 3,673 HC patients. Sociocultural processes (i.e., lack of attention to early clinical signs in women or diagnostic bias) may account for the delay. However, Dimitrow et al[3] reported that not just the diagnosis but also the onset of symptoms was delayed in females with HC. Therefore, differences in sexual hormones and gene expression may play a role.[27]

Female patients were older and had different clinical and phenotypic features including more hypertension, more LV outflow obstruction, and a higher indexed MWT. Indeed, hypertensive HC is known to occur predominantly in the elderly, particularly female.[28] Krumholz et al[29] reported that women adapt differently to hypertension than men, namely women develop concentric hypertrophy with normal or reduced LV size and men develop LV dilation without increased LV wall thickness. It may be due to these differences that LV outflow obstruction was more common in female patients. In addition, the underlying HC mutation most likely has an important impact on the phenotypic expression of HC. Bos et al[7] demonstrated that patients with sigmoidal HC were generally older women with hypertension and LV outflow obstruction. The majority of these patients were mutation negative, in contrast to patients with reverse curve HC where 80% were mutation positive.[30] This study extends these findings by showing that women ≥70 years old had a significantly less genetic

Table 4
Multivariate Cox proportional hazard regression analyses for all-cause and cardiovascular mortality

Variable	All-cause mortality		Cardiovascular mortality	
	HR (95% CI)	p value	HR (95% CI)	p value
Female gender	1.25 (0.91-1.73)	0.16	1.22 (0.83-1.79)	0.31
Age at evaluation	1.03 (1.01-1.04)	<0.001	1.00 (0.98-1.02)	0.95
Diagnosis by routine examination	0.83 (0.53-1.28)	0.38	0.74 (0.45-1.22)	0.24
Arterial hypertension	0.92 (0.65-1.30)	0.63	0.78 (0.50-1.21)	0.27
Atrial fibrillation	1.24 (0.89-1.71)	0.19	2.01 (1.3-2.98)	<0.001
Abnormal systolic function	2.94 (2.02-4.29)	<0.001	3.26 (2.09-5.10)	<0.001
MWT/BSA (mm/m^2)	1.00 (0.92-1.08)	0.91	1.02 (0.94-1.11)	0.65
Left atrial size/BSA (mm/m^2)	1.06 (1.02-1.10)	0.003	1.06 (1.02-1.11)	0.006
Pathogenic mutation	0.90 (0.61-1.32)	0.57	1.02 (0.63-1.67)	0.92

Hazard ratios (HR) were calculated using multivariable Cox proportional hazard regression models with adjustment for family relatedness. BSA = body surface area; CI = confidence interval; HR = hazard ratio; MWT = maximal wall thickness.

Table 5
Multivariate Cox proportional hazard regression analyses for SCD/aborted SCD and HF-related mortality

Variable	SCD/aborted SCD		HF related mortality	
	HR (95% CI)	p value	HR (95% CI)	p value
Female gender	0.75 (0.44-1.30)	0.31	1.77 (0.95-3.27)	0.08
Age at evaluation	0.99 (0.97-1.01)	0.22	1.00 (0.97-1.03)	0.91
Atrial fibrillation	1.42 (0.80-2.56)	0.24	3.73 (1.84-7.55)	<0.001
Abnormal systolic function	2.58 (1.36-4.93)	0.004	6.80 (3.42-13.50)	<0.001
MWT/BSA (mm/m^2)	1.06 (0.95-1.17)	0.30	-	-
LA size/BSA (mm/m^2)	1.05 (0.99-1.11)	0.12	1.10 (1.03-1.19)	0.009
Pathogenic mutation	1.03 (0.56-1.90)	0.93	1.05 (0.48-2.28)	0.91

Hazard ratios (HR) were calculated using multivariable Cox proportional hazard regression models with adjustment for family relatedness. BSA = body surface area; CI = confidence interval; HF = heart failure; HR = hazard ratio; MWT = maximal wall thickness; SCD = sudden cardiac death.

yield in comparison to men. Mutation-negative HC might culminate from a multifactorial process involving undefined genetic and environmental factors.[20]

At baseline, female patients showed more signs of adverse remodeling than male patients (systolic and diastolic impairment, larger indexed left atria and larger LV). Whether female patients with HC are indeed at a higher risk of HF is currently unknown. Unlike previous studies,[15,16,18,19] we did not observe an increased risk of HF related mortality or hospital admission for HF in female patients during follow-up. The discrepancy with previous studies may be caused by the use of different end points. Studies that assessed LV contractility in similarly aged male and female patients with HC also reported conflicting results. Dimitrow et al[6] measured fractional shortening in 77 males and 52 females with HC, and found no gender difference (45% vs 44%, $p > 0.05$). Kubo et al[11] described a higher fractional shortening in 88 female patients versus 173 male patients (43% vs 40%, $p = 0.01$).

In the present study, there was no independent association between gender and all-cause mortality, cardiovascular mortality, HF-related death, or SCD and/or aborted SCD. Important predictors of outcome were age at evaluation, abnormal systolic function, left atrial size adjusted for body surface area, and atrial fibrillation. Previous studies have also demonstrated a prognostic value for these variables in patients with HC.[31–33] The variables combined represent part of a distinct disease pathway termed "stage III, adverse remodeling."[34] About 15% to 20% of the patients with HC follow this pathway and are at increased risk of death.[34] Previous studies that assessed gender and mortality in HC have reported conflicting results.[5,15–17] Similar to our results, Olivotto et al[15] found no association between gender and all-cause mortality, HC-related death, or SCD among 969 patients with HC after 6.2-year follow-up. However, they found an association between female gender and the combined end point of progression to NYHA class III or IV or death from HF or stroke.[15] Terauchi et al[19] studied gender differences among 50 patients with HC caused by *MYBPC3* mutations and reported more HF events in female patients, however, no gender difference regarding survival. Dimitrow et al[5] reported no survival difference between 111 male and 70 female patients with HC during 7-year follow-up. In contrast to these studies, Wang et al[16] found female gender to be independently associated with all-cause mortality (HR 2.19, $p = 0.01$), cardiovascular death (HR 2.19, $p = 0.01$), and progression to HF (HR 1.73, $p = 0.01$) during 4-year follow-up of 621 patients with HC. Of note, in that study, patients with HF at baseline were excluded. Geske et al[17] demonstrated that female gender was an independent predictor of all-cause mortality (HR 1.13, $p = 0.01$) during 11-year follow-up of 3,673 patients with HC. The discrepancy with previous studies was suggested to be caused by their larger, sicker cohort.[17]

Overall, the findings in the present study illustrate that there is a significant delay in the clinical presentation of

Table 6
Differences in interventions and nonfatal clinical events in male and female patients with hypertrophic cardiomyopathy during follow-up

Variables	Overall (n = 691)	Male (n = 431)	Female (n = 260)	HR (95% CI)	p value
Septal reduction therapy	223 (32%)	131 (30%)	92 (36%)	1.29 (0.98-1.69)	0.07
Surgical myectomy	173 (25%)	101 (23%)	72 (28%)	1.32 (0.97-1.79)	0.08
Alcohol septal ablation	63 (9%)	38 (9%)	25 (10%)	1.13 (0.68-1.87)	0.64
ICD implantation	155 (23%)	102 (24%)	53 (21%)	0.89 (0.64-1.24)	0.49
PM implantation	29 (4%)	14 (3%)	15 (6%)	1.96 (0.95-4.01)	0.07
AF de novo	49 (9%)	36 (11%)	13 (7%)	0.66 (0.36-1.23)	0.19
Stroke	22 (3%)	13 (3%)	9 (4%)	1.22 (0.52-2.85)	0.65
TIA	23 (3%)	17 (4%)	6 (2%)	0.57 (0.23-1.42)	0.23
HF admission	44 (6%)	22 (5%)	22 (9%)	1.71 (0.95-3.07)	0.07

Data are expressed as absolute n (%). Hazard ratios (HR) were calculated using univariable Cox proportional hazard regression models with adjustment for family relatedness.

AF = atrial fibrillation; HF = heart failure; ICD = implantable cardioverter defibrillator; PM = pacemaker; TIA = transient ischemic attack.

female patients with HC and that female patients present with more advanced disease than male patients. Similar observations were made for patients with coronary artery disease, which is partly attributable to gender-specific differences in the sensitivity of diagnostic procedures.[27] In the present study, adjusting echocardiographic parameters to body surface area revealed a worse phenotype than we suspected based on unadjusted parameters, suggesting a diagnostic bias. By applying gender- or body surface area-adjusted parameters, we may be able to recognize disease progression earlier, resulting in more intense follow-up and management and potentially a better outcome. Future studies are needed to investigate this further.[9]

This study has several limitations. First, this is a retrospective study that has inherent limitations. Second, the patients were referred to a tertiary center for cardiomyopathy, which may have caused a selection bias. Third, the prevalence of Dutch *MYBPC3* founder mutations in the Netherlands is relatively high,[35] which may affect extrapolation of the findings to other countries. And fourth, follow-up for the occurrence of nonfatal clinical events was available in only 69%, due to follow-up in other hospitals.

In conclusion, female patients with HC present at a more advanced age with a different clinical, phenotypic, and genetic status. There is no independent association between female gender and all-cause mortality, cardiovascular mortality, HF-related mortality, or SCD.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary materials associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2018.08.040.

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